REMARKS

Reconsideration of the application in light of the amendments and the following remarks is respectfully requested.

I. Status of the Claims

Upon entry of this amendment, claims 1–52 are pending in this application. As claims 3–10, 15–19, and 24–47 were previously withdrawn from consideration by the Examiner, claims 1, 2, 11–14, 20–23, and 48–52 are at issue. Claims 2, 12, 21–23 have been allowed. Claim 1 has been amended to no longer call for solvates. Support for amended claim 1 can be found in claims 1 and 2, as originally filed. Claims 48–52 have been added. Support for new claims 48–52 can be found in claims 1 and 2 as filed, and on p. 5, ll. 1–6, of the specification, as filed. No new matter has been added by way of this amendment.

II. Enablement Rejection

Claims 1, 11, 13, 14 and 20 are rejected for allegedly lacking enablement. The standard for enablement is whether the application contains sufficient information to enable one of ordinary skill in the pertinent art to make and use the claimed invention without undue experimentation. Among the factors to be considered in determining whether the claims are enabled is the amount of guidance provided in the application and the level of ordinary skill in the art. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

In the Office Action, the Examiner argues that "*there is no evidence that solvates of these [claimed] compounds actually exist, if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.*" (Official Action, p. 3). Without conceding the validity of this rejection, and in the interest of advancing prosecution, Applicant has deleted "solvates" from the claims.

The Examiner states that the reagents taught on pp. 11–12 of the specification cannot form all the salts of the claimed compounds. However, the cited section teaches an extraction

process, not a salt forming process. The extraction process is separate from the salt or anhydride forming process. Pages 6 and 7 of the specification, as filed, provide ample guidance to one of ordinary skill in the art regarding the reagents and process for forming salts of the present invention. Upon reading this disclosure, one of ordinary skill in the art would have readily been able to make and use salts of the compounds of claim 1.

Additionally, one of ordinary skill in the art would have readily known how to form tautomers and anhydrides of the present invention. As a general matter, the level of skill in the chemical arts is high. Typically, the ordinary skilled artisan is a Ph.D. chemist with 2–3 years experience. The most basic form of tautomerization, keto–enol tautomerization, is taught in undergraduate organic chemistry classes. For the Examiner's reference, an undergraduate level organic chemistry textbook excerpt, describing how to perform such a reaction, is submitted herewith as Exhibit 1.[1] Graduate level organic chemistry texts teach other mechanisms of tautomerization (*see* Exhibit 2).[2] Accordingly, the tautomerization reactions set out in Exhibits 1 and 2 are within the skill of the ordinary skilled organic chemist.

By the same reasoning, one of ordinary skill in the art would have readily known how to form anhydrides of the present invention. As stated above, the ordinary skilled chemist is typically a Ph.D. with 2–3 years experience. Graduate level organic chemistry texts provide great detail as to how to form various anhydrides, depending on a molecule's atomic structure. For the Examiner's convenience, an excerpt from a graduate level organic chemistry textbook is submitted herewith, as Exhibit 3.[3] Exhibit 3 clearly shows that multiple methods of anhydride formation are taught to organic chemistry graduate students. Accordingly, one of ordinary skill in the art would have known how to form the claimed anhydrides of the present invention.

For at least these reasons, Applicant requests withdrawal of the enablement rejection and reconsideration of the claims.

---

[1] Exhibit 1 published in 1999, which is approximately five years before the present application's filing date (2004).
[2] Exhibit 2 published in 1992, which is approximately twelve years before the present application's filing date (2004).
[3] Exhibit 3 published in 1992, which is approximately twelve years before the present application's filing date (2004).

III. Written Description Rejection

Claims 1, 11, 13, 14 and 20 are rejected for allegedly lacking written description. Specifically, the Examiner states that the specification does not have written description for halogen, amine, amino, imino, carboxylic acid or amide substitutions at positions 1, 4, 5, or 8 of the alkaloid derivative, as called for in claim 1. To satisfy the written description requirement, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Vas–Cath Inc. v. Mahurkar, 935 F. 2d 1555, 1563 (Fed. Cir. 1991).

The Examiner's rejection is not well taken for at least the following reason. The specification clearly states that the invention may have substitutions at C–1, C–4, C–5 or C–8, and that the substituents can be halogens, amino, imino, carboxylic acid or amides (Specification as filed, p. 5, ll. 4–6). Therefore, contrary to the Examiner's assertion, the optional substituents should not be considered new matter (Official Action, p. 4). Further, upon reading this disclosure, one of ordinary skill in the art would readily understand the breadth of these classes of substituents and where the substituents can be located in the compound. Therefore, one of ordinary skill in the art would recognize that the inventors had possession of the aforementioned substituted compounds at the time the present application was filed.

Accordingly, Applicant requests withdrawal of the written description rejection and reconsideration of the claims.

IV. Allowed Claims

In the Official Action, the Examiner states that claims 2, 12 and 21–23 are found to be allowable (Official Action, p. 4). As claims 15–18, 38, 41–42 and 44–47 require all the limitations of claim 2, Applicant requests rejoinder of these claims.

V. New Claims 48–52

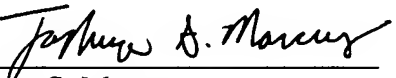
Claims 48–52 have been added. Claim 48 is directed to the same subject matter as claim 1, except claim 48 does not call for any "optional substituents." Claims 49–52 depend from claim 48. Claims 48–52 are believed to be free of the prior art and in condition for allowance.

CONCLUSION

In view of the above remarks, Applicants believe the pending application is in condition for allowance. If there are any remaining issues that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is kindly requested to contact the undersigned at the telephone number indicated below.

Dated: March 25, 2009

Respectfully submitted,

By 

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Exhibits

- Exhibit 1 – 7 pages
- Exhibit 2 – 7 pages
- Exhibit 3 – 3 pages

Exhibit 1

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L. G. Wade, Jr.
Whitman College

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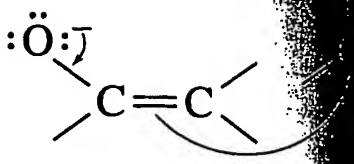
CHAPTER 22

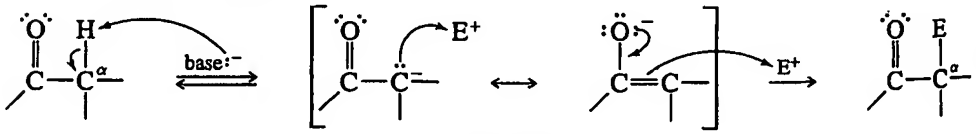
Alpha Substitutions and Condensations of Enols and Enolate Ions



22-1 Introduction

Up to now, we have studied two of the main types of carbonyl reactions: nucleophilic addition and nucleophilic acyl substitution. In these reactions, the carbonyl group serves as an *electrophile* by accepting electrons from an attacking nucleophile. In this chapter, we consider two more types of reactions: substitution at the carbon atom next to the carbonyl group (called alpha substitution) and carbonyl condensations. **Alpha (α) substitutions** involve the replacement of a hydrogen atom at the α carbon atom (the carbon next to the carbonyl) by some other group. Alpha substitution generally takes place when the carbonyl compound is converted to its enolate ion or enol tautomer. Both of these have lost a hydrogen atom at the alpha position, and both are *nucleophilic*. Attack on an electrophile completes the substitution.

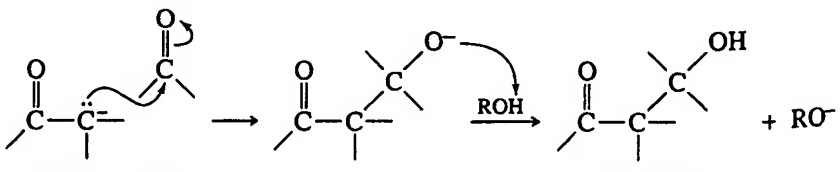
Alpha substitution



enolate ion

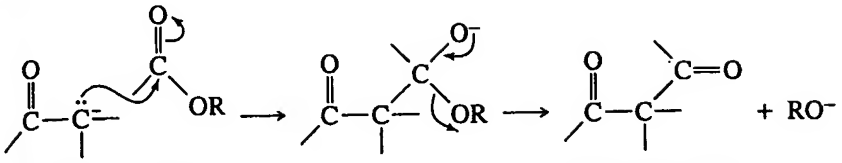
Carbonyl **condensations** are alpha substitutions where the electrophile is another carbonyl compound. From the electrophile's point of view, the condensation is either a nucleophilic addition or a nucleophilic acyl substitution. With ketones and aldehydes, protonation of the alkoxide gives the product of nucleophilic addition. With esters, loss of alkoxide gives the product of nucleophilic acyl substitution.

Condensation: Addition to ketones and aldehydes



enolate ketone addition product

Condensation: Substitution with esters



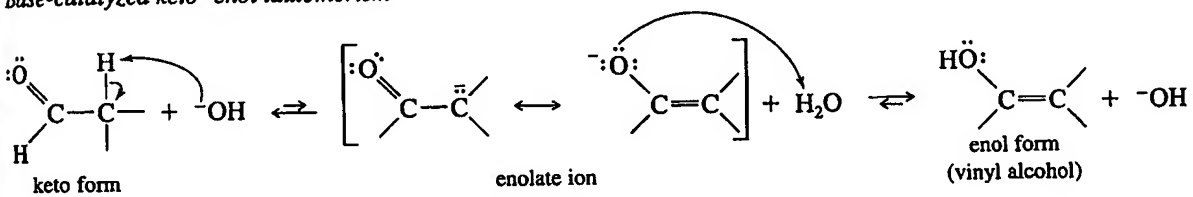
Alpha substitutions and condensations of carbonyl compounds are some of the most common methods for forming carbon–carbon bonds. A wide variety of compounds can participate as nucleophiles or electrophiles (or both) in these reactions, and many useful products can be synthesized. We begin our study of these reactions by considering the structure and formation of enols and enolate ions.

22-2 Enols and Enolate Ions

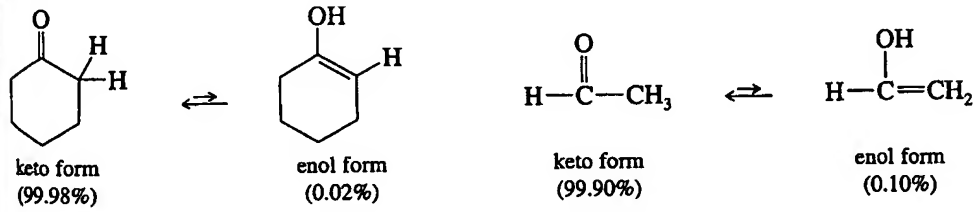
22-2A Keto–Enol Tautomerism

In the presence of strong bases, ketones and aldehydes act as weak proton acids. A proton on the α carbon is abstracted to form a resonance-stabilized **enolate ion** with the negative charge spread over a carbon atom and an oxygen atom. Reprotonation can occur either on the α carbon (returning to the **keto** form) or on the oxygen atom, giving a vinyl alcohol, the **enol** form.

Base-catalyzed keto–enol tautomerism



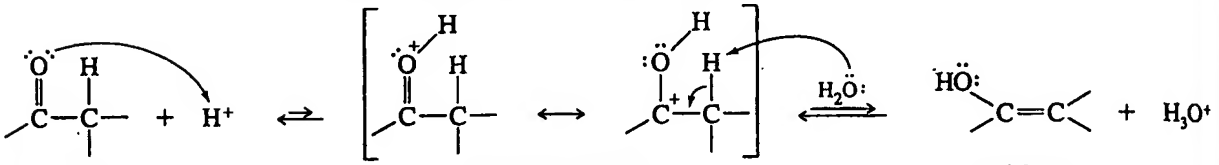
In this way, base catalyzes an equilibrium between isomeric keto and enol forms of a carbonyl compound. For simple ketones and aldehydes, the keto form predominates. Therefore, a vinyl alcohol (an enol) is best described as an alternative isomeric form of a ketone or aldehyde. In Section 9-9, we saw that an enol intermediate, formed by hydrolysis of an alkyne, quickly isomerizes to its keto form.



This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called **tautomerism,** and the isomers that interconvert are called **tautomers.** Don't confuse tautomers with resonance forms. Tautomers are true isomers (different compounds) with their atoms arranged differently. Under the right circumstances, with no catalyst present, either individual tautomeric form may be isolated. Resonance forms are different representations of the *same* structure, with all the atoms in the same places, showing how the electrons are delocalized.

Keto–enol tautomerism is also catalyzed by acid. In acid, a proton is moved from the α carbon to oxygen by first protonating oxygen and then removing a proton from carbon.

Acid-catalyzed keto–enol tautomerism

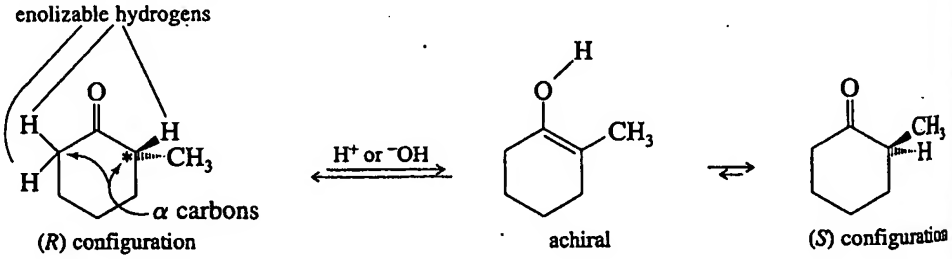


PROBLEM-SOLVING HINT

In acid, proton transfers usually occur by adding a proton in the new position, then deprotonating the old position; in base, by deprotonating the old position, then reprotonating at the new position.

Compare the base-catalyzed and acid-catalyzed mechanisms shown above for keto–enol tautomerism. In base, the proton is removed from carbon, then replaced on oxygen. In acid, oxygen is protonated first, then carbon is deprotonated. Most proton-transfer mechanisms work this way. In base, the proton is removed from the old location, then replaced at the new location. In acid, protonation occurs at the new location, followed by deprotonation at the old location.

In addition to its mechanistic importance, keto–enol tautomerism affects the stereochemistry of ketones and aldehydes. A hydrogen atom on an α carbon may be lost and regained through keto–enol tautomerism; such a hydrogen is said to be **enolizable.** If a chiral carbon has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. A racemic mixture (or an equilibrium mixture of diastereomers) is the result.



PROBLEM 22-1

Phenylacetone can form two different enols.

(a) Show the structures of these enols.
(b) Predict which enol will be present in the larger concentration at equilibrium.
(c) Give mechanisms for the formation of the two enols in acid and in base.

PROBLEM 22-2

Show each step in the mechanism of the acid-catalyzed interconversion of *(R)*- and *(S)*-2-methylcyclohexanone.

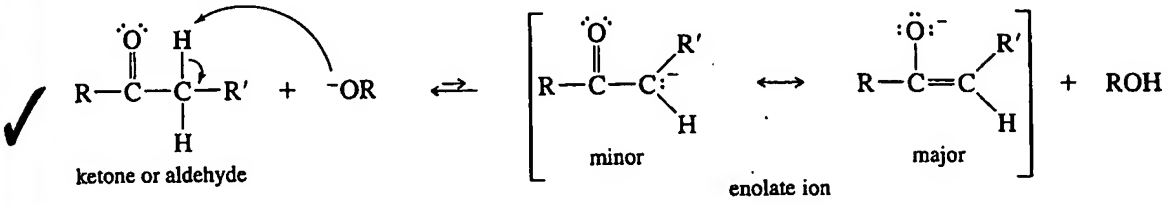
PROBLEM 22-3

When *cis*-2,4-dimethylcyclohexanone is dissolved in aqueous ethanol containing a trace of NaOH, a mixture of cis and trans isomers results. Give a mechanism for this isomerization.

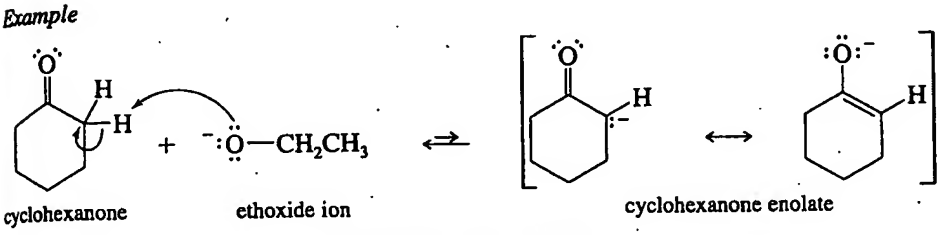
22-2B Formation and Stability of Enolate Ions

A carbonyl group dramatically increases the acidity of the protons on the α-carbon atom because most of the enolate ion's negative charge resides on the electronegative oxygen atom. The pK_a for removal of an α proton from a typical ketone

or aldehyde is about 20, showing that a typical ketone or aldehyde is much more acidic than an alkane or an alkene ($pK_a > 40$), or even an alkyne ($pK_a = 25$). Still, a ketone or aldehyde is less acidic than water ($pK_a = 15.7$) or an alcohol ($pK_a = 16$ to 19) When a simple ketone or aldehyde is treated with hydroxide ion or an alkoxide ion, the equilibrium mixture contains only a small fraction of the deprotonated, enolate form.

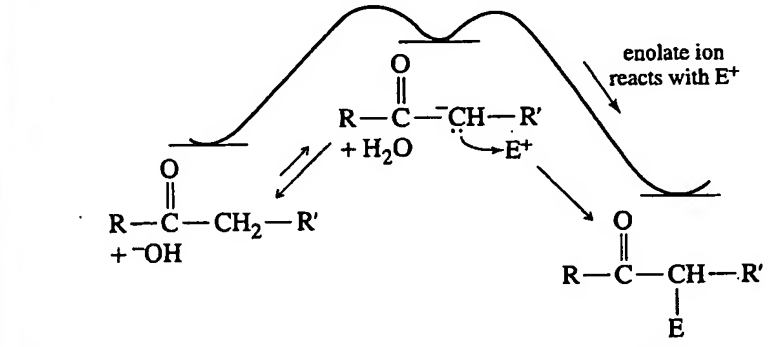


Example



(equilibrium lies to the left)

Even though the equilibrium concentration of the enolate ion may be small, it serves as a useful, reactive nucleophile. When an enolate reacts with an electrophile (other than a proton), the enolate concentration decreases, and the equilibrium shifts to the right (Fig. 22-1). Eventually, all the carbonyl compound reacts via a low concentration of the enolate ion.



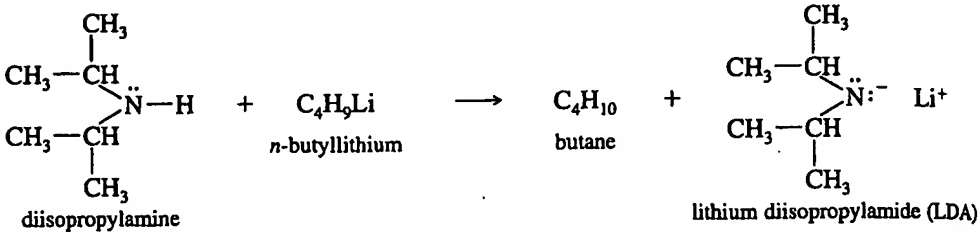
◀ Figure 22-1
Reaction of the enolate ion with an electrophile removes it from equilibrium.

PROBLEM 22-4

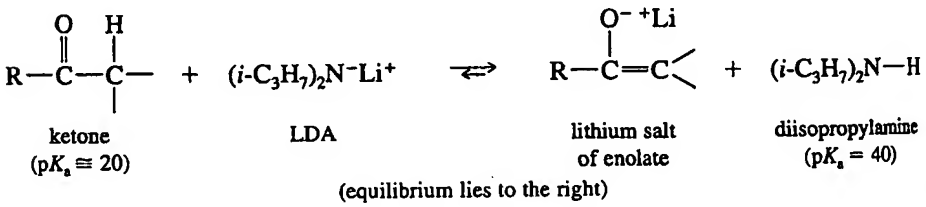
Give the important resonance forms for the enolate ion of
(a) acetone (b) cyclopentanone (c) 2,4-pentanedione

Sometimes this equilibrium mixture of enolate and base won't work, usually because the base (hydroxide or alkoxide) reacts with the electrophile faster than the enolate does. In these cases, we need a base that reacts completely to convert the carbonyl compound to its enolate before adding the elecrophile. Although sodium hydroxide

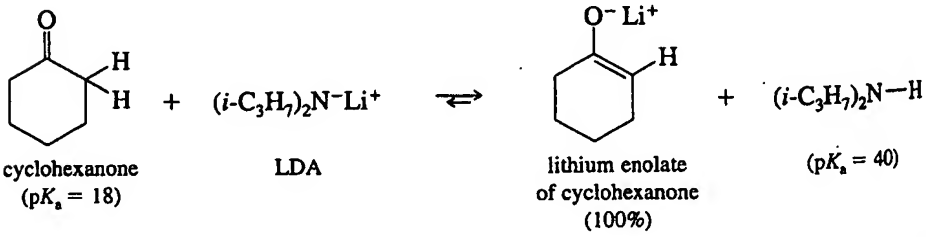
and alkoxides are not sufficiently basic, powerful bases are available to convert a carbonyl compound completely to its enolate. The most effective and useful base for this purpose is lithium diisopropylamide (LDA), the lithium salt of diisopropylamine. LDA is made by using an alkyllithium reagent to deprotonate diisopropylamine.



Diisopropylamine has a pK_a of about 40, showing that it is much *less* acidic than a typical ketone or aldehyde. By virtue of its two isopropyl groups, LDA is a bulky reagent; it does not easily attack a carbon atom or add to a carbonyl group. Thus it is a powerful base, but not a strong nucleophile. When LDA reacts with a ketone, it abstracts the α proton to form the lithium salt of the enolate. We will see that these lithium enolate salts are very useful in synthesis.



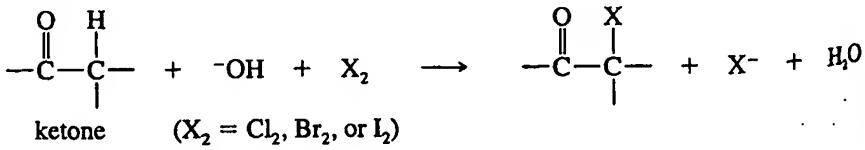
Example



22-3 Alpha Halogenation of Ketones

22-3A Base-Promoted α Halogenation

When a ketone is treated with a halogen and base, an α-halogenation reaction occurs.



Example

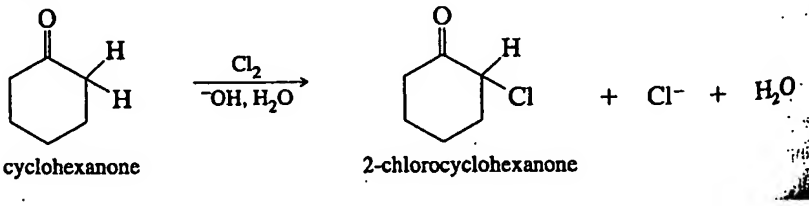


Exhibit 2

ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University

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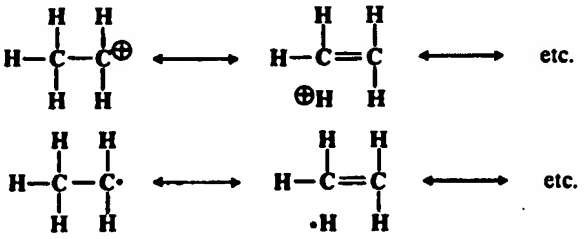
For the other alkyl groups, hyperconjugation is diminished because the number of C—H bonds is diminished and in *t*-butyl there are none; hence, with respect to this effect, methyl is the strongest electron donor and *t*-butyl the weakest.

However, the Baker–Nathan effect has now been shown not to be caused by hyperconjugation, but by differential solvation.[256] This was demonstrated by the finding that in certain instances where the Baker–Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.[257] Since the molecular structures are unchanged in going from the gas phase into solution, it is evident that the Baker–Nathan order in these cases is not caused by a structural feature (hyperconjugation) but by the solvent. That is, each alkyl group is solvated to a different extent.[258]

At present the evidence is against hyperconjugation in the ground states of neutral molecules.[259] However, for carbocations and free radicals[260] and for excited states of molecules,[261] there is evidence that hyperconjugation is important. In hyperconjugation in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation*,[262] the canonical forms involve not only no-bond resonance but also a charge separation not possessed by the main form. In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*:



Even here the main form contributes more to the hybrid than the others.

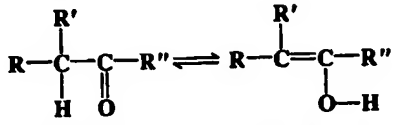
TAUTOMERISM

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[263] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another.

[256]This idea was first suggested by Schubert; Sweeney *J. Org. Chem.* **1956**, *21*, 119.
[257]Hehre; McIver; Pople; Schleyer *J. Am. Chem. Soc.* **1974**, *96*, 7162; Arnett; Abboud *J. Am. Chem. Soc.* **1975**, *97*, 3865; Glyde; Taylor *J. Chem. Soc., Perkin Trans. 2* **1977**, 678. See also Taylor *J. Chem. Res. (S)* **1985**, 318.
[258]For an opposing view, see Cooney; Happer *Aust. J. Chem.* **1987**, *40*, 1537.
[259]For some evidence in favor, see Laube; Ha *J. Am. Chem. Soc.* **1988**, *110*, 5511.
[260]Symons *Tetrahedron* **1962**, *18*, 333.
[261]Rao; Goldman; Balasubramanian *Can. J. Chem.* **1960**, *38*, 2508.
[262]Muller; Mulliken *J. Am. Chem. Soc.* **1958**, *80*, 3489.
[263]For reviews, see Toullec *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77; Kol'tsov; Kheifets *Russ. Chem. Rev.* **1971**, *40*, 773-788, **1972**, *41*, 452-467; Forsén; Nilsson in Zabicky, Ref. 246, vol. 2, pp. 157-240.

Keto-Enol Tautomerism[264]

A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:[264a]



Keto form Enol form

In simple cases (R″ = H, alkyl, OR, etc.) the equilibrium lies well to the left (Table 2.1). The reason can be seen by examining the bond energies in Table 1.7. The keto form differs from the enol form in possessing a C—H, a C—C, and a C=O bond where the enol has a C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal/mol (1500 kJ/mol) and of the second three is 347 kcal/mol (1452 kJ/mol). The keto form is therefore thermodynamically more stable by about 12 kcal/mol (48 kJ/mol) and enol forms cannot normally be isolated.[272a] In certain cases, however, a larger amount of the enol form

TABLE 2.1 The enol content of some carbonyl compounds

Compound	Enol content, %	Ref.
Acetone	6×10^{-7}	265
$PhCOCH_3$	1.1×10^{-6}	266
Cyclopentanone	1×10^{-6}	267
CH_3CHO	6×10^{-5}	268
Cyclohexanone	4×10^{-5}	267
Butanal	5.5×10^{-4}	269
$(CH_3)_2CHCHO$	1.4×10^{-2}	270
Ph_2CHCHO	9.1	271
CH_3COOEt	No enol found[a]	267
CH_3COCH_2COOEt	8.4	272
$CH_3COCH_2COCH_3$	80	272
$PhCOCH_2COCH_3$	89.2	267
$EtOOCCH_2COOEt$	7.7×10^{-3}	267
$NCCH_2COOEt$	2.5×10^{-1}	267

[a]Less than 1 part in 10 million.

[264]The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction 2-3).

[264a]For a treatise, see Rappoport *The Chemistry of Enols*; Wiley: New York, 1990.

[269]Tapuhi; Jencks *J. Am. Chem. Soc.* 1982, *104*, 5758; Chiang; Kresge; Tang; Wirz *J. Am. Chem. Soc.* 1984, *106*, 460. See also Hine; Arata *Bull. Chem. Soc. Jpn.* 1976, *49*, 3089; Guthrie *Can. J. Chem.* 1979, *57*, 797, 1177; Dubois; El-Alaoui; Toullec *J. Am. Chem. Soc.* 1981, *103*, 5393; Toullec *Tetrahedron Lett.* 1984, *25*, 4401; Chiang; Kresge; Schepp *J. Am. Chem. Soc.* 1989, *111*, 3977.

[266]Keeffe; Kresge; Toullec *Can. J. Chem.* 1986, *64*, 1224.

[267]Gero *J. Org. Chem.* 1954, *19*, 469, 1960; Keeffe, Kresge; Schepp *J. Am. Chem. Soc.* 1990, *112*, 4862. See these papers for values for other simple compounds.

[268]Chiang; Hojatti; Keeffe; Kresge; Schepp; Wirz *J. Am. Chem. Soc.* 1987, *109*, 4000.

[269]Bohne; MacDonald; Dunford *J. Am. Chem. Soc.* 1986, *108*, 7867.

[270]Chiang; Kresge; Walsh *J. Am. Chem. Soc.* 1986, *108*, 6314; Ref. 269.

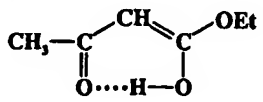
[271]Chiang; Kresge; Krogh *J. Am. Chem. Soc.* 1988, *110*, 2600.

[272]Moriyasu; Kato; Hashimoto *J. Chem. Soc., Perkin Trans. 2* 1986, 515.

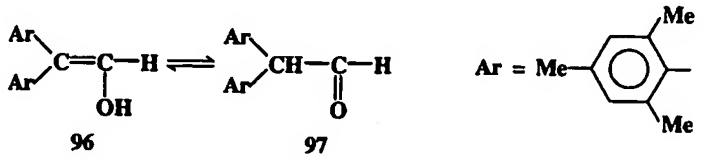
[272a]For reviews on the generation of unstable enols, see Kresge *Pure Appl. Chem.* 1991, *63*, 213-221; Capon, in Rappoport, Ref. 264a, pp. 307-322.

is present, and it can even be the predominant form.[273] There are three main types of the more stable enols:[274]

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. As the table shows, carboxylic esters have a much smaller enolic content than ketones. In molecules like acetoacetic ester, the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



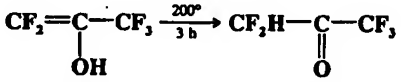
2. Molecules that contain two or three bulky aryl groups.[275] An example is 2,2-dimesitylethenol (**96**). In this case the keto content at equilibrium is only 5%.[276] In cases



96 **97**

such as this steric hindrance (p. 161) destabilizes the keto form. In **96** the two aryl groups are about 120° apart, but in **97** they must move closer together (~109.5°). Such compounds are often called *Fuson-type enols*.[277]

3. Highly fluorinated enols, an example being **98**.[278]



98 **99**

In this case the enol form is not more stable than the keto form (it is less stable, and converts to the keto form upon prolonged heating). It can however be kept at room temperature for long periods of time because the tautomerization reaction (**2-3**) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39°C, while the enol is a liquid even at −78°C. Each can be kept at room temperature for days if catalysts such as acids or bases are rigorously excluded.[279] Even the simplest enol, vinyl alcohol CH_2=CHOH, has been prepared in the

[273]For reviews of stable enols, see Kresge *Acc. Chem. Res.* **1990**, *23*, 43-48, *CHEMTECH*, **1986**, 250-254; Hart; Rappoport; Biali, in Rappoport, Ref. 264a, pp. 481-589; Hart, *Chem. Rev.* **1979**, *79*, 515-528; Hart; Sasaoka *J. Chem. Educ.* **1980**, *57*, 685-688.

[274]For some examples of other types, see Pratt; Hopkins *J. Am. Chem. Soc.* **1987**, *109*, 5553; Nadler; Rappoport; Arad; Apeloig *J. Am. Chem. Soc.* **1987**, *109*, 7873.

[275]For a review, see Rappoport; Biali *Acc. Chem. Res.* **1988**, *21*, 442-449. For a discussion of their structures, see Kaftory; Nugiel; Biali; Rappoport *J. Am. Chem. Soc.* **1989**, *111*, 8181.

[276]Biali; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 1007. See also Kaftory; Biali; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 1701; Nugiel; Rappoport *J. Am. Chem. Soc.* **1985**, *107*, 3669; Nadler; Rappoport *J. Am. Chem. Soc.* **1987**, *109*, 2112; O'Neill; Hegarty *J. Chem. Soc., Chem. Commun.* **1987**, 744; Becker; Andersson *Tetrahedron Lett.* **1987**, *28*, 1323.

[277]First synthesized by Fuson; see for example Fuson; Southwick; Rowland *J. Am. Chem. Soc.* **1944**, *66*, 1109.

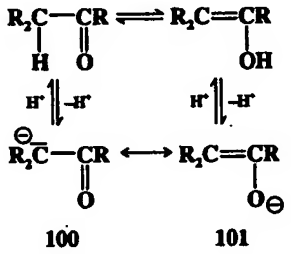
[278]For a review, see Bekker; Knunyants *Sov. Sci. Rev. Sect. B* **1984**, *5*, 145-182.

[279]For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg *J. Am. Chem. Soc.* **1968**, *90*, 7008.

gas phase at room temperature, where it has a half-life of about 30 min.[280] The enol $Me_2C{=}CCHOH$ is indefinitely stable in the solid state at −78°C and has a half-life of about 24 hours in the liquid state at 25°C.[281]

The extent of enolization[281a] is greatly affected by solvent,[282] concentration, and temperature. Thus, acetoacetic ester has an enol content of 0.4% in water and 19.8% in toluene.[283] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. As an example of the effect of temperature, the enol content of pentan-2,4-dione $CH_3COCH_2COCH_3$ was found to be 95, 68, and 44%, respectively, at 22, 180, and 275°C.[284]

When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **100** and **101** differ only in



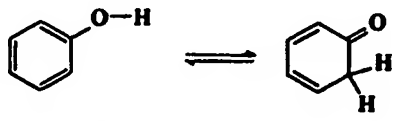
100 **101**

placement of electrons, *they* are not tautomers but canonical forms. The true structure of the enolate ion is a hybrid of **100** and **101** although **101** contributes more, since in this form the negative charge is on the more electronegative atom.

Other Proton-Shift Tautomerism

In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:[285]

1. Phenol-keto tautomerism.[286]



Phenol Cyclohexadienone

[280]Saito *Chem. Phys. Lett.* **1976**, *42*, 399. See also Capon; Rycroft; Watson; Zucco *J. Am. Chem. Soc.* **1981**, *103*, 1761; Holmes; Lossing *J. Am. Chem. Soc.* **1982**, *104*, 2648; McGarrity; Cretton; Pinkerton; Schwarzenbach; Flack *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 405 [*Angew. Chem. 95*, 426]; Rodler; Blom; Bauder *J. Am. Chem. Soc.* **1984**, *106*, 4029; Capon; Guo; Kwok; Siddhanta; Zucco *Acc. Chem. Res.* **1988**, *21*, 135-140.

[281]Chin; Lee; Park; Kim *J. Am. Chem. Soc.* **1988**, *110*, 8244.

[281a]For a review of keto-enol equilibrium constants, see Toullec, in Rappoport, Ref. 264a, pp. 323-398.

[282]For an extensive study, see Mills; Beak *J. Org. Chem.* **1985**, *50*, 1216.

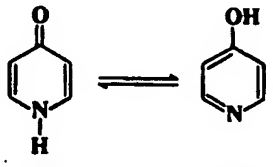
[283]Meyer *Leibigs Ann. Chem.* **1911**, *380*, 212. See also Ref. 272.

[284]Hush; Livett; Peel; Willett *Aust. J. Chem.* **1987**, *40*, 599.

[285]For a review of the use of x-ray crystallography to determine tautomeric forms, see Furmanova *Russ. Chem. Rev.* **1981**, *50*, 775-791.

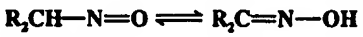
[286]For reviews, see Ershov; Nikiforov *Russ. Chem. Rev.* **1966**, *35*, 817-833; Forsén; Nilsson, Ref. 263, pp. 168-198.

For most simple phenols this equilibrium lies well to the side of the phenol, since only on that side is there aromaticity. For phenol itself there is no evidence for the existence of the keto form.[287] However, the keto form becomes important and may predominate: (1) where certain groups, such as a second OH group or an N=O group, are present;[288] (2) in systems of fused aromatic rings;[289] (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[290] although in vapor phase the positions of many of these equilibria are reversed.[291] For example, in the equilibrium between 4-pyridone (**102**) and 4-hydroxypyridine (**103**), **102** is the only form detectable in ethanolic solution, while **103** predominates in the vapor phase.[291]



102 **103**

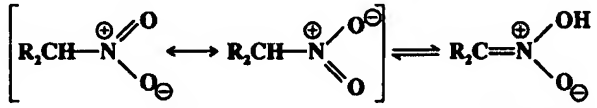
2. Nitroso-oxime tautomerism.



Nitroso Oxime

This equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is no α hydrogen.

3. Aliphatic nitro compounds are in equilibrium with aci forms.



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine-enamine tautomerism.[292]

Imine Enamine

[287]Keto forms of phenol and some simple derivatives have been generated as intermediates with very short lives, but long enough for spectra to be taken at 77 K. Lasne; Ripoll; Denis *Tetrahedron Lett.* **1980**, *21*, 463. See also Capponi; Gut; Wirz *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 344 [*Angew. Chem. 98*, 358].

[288]Ershov; Nikiforov, Ref. 286. See also Highet; Chou *J. Am. Chem. Soc.* **1977**, *99*, 3538.

[289]See, for example, Majerski; Trinajstić *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2648.

[290]For a monograph on tautomerism in heterocyclic compounds, see Elguero; Marzin; Katritzky; Linda *The Tautomerism of Heterocycles*; Academic Press: New York, 1976. For reviews, see Katritzky; Karelson; Harris *Heterocycles* **1991**, *32*, 329-369; Beak *Acc. Chem. Res.* **1977**, *10*, 186-192; Katritzky *Chimia* **1970**, *24*, 134-146.

[291]Beak; Fry; Lee; Steele *J. Am. Chem. Soc.* **1976**, *98*, 171.

[292]For reviews, see Shainyan; Mirskova *Russ. Chem. Rev.* **1979**, *48*, 107-117; Mamaev; Lapachev *Sov. Sci. Rev. Sect. B.* **1985**, *7*, 1-49. The second review also includes other closely related types of tautomerization.

Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[293]

Ring-chain tautomerism[294] (as in sugars) consists largely of cyclic analogs of the previous examples. There are many other highly specialized cases of proton-shift tautomerism.

Valence Tautomerism

This type of tautomerism is discussed on p. 1134.

[293]For examples of the isolation of primary and secondary enamines, see Shin; Masaki; Ohta *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1657; de Jeso; Pommier *J. Chem. Soc., Chem. Commun.* **1977**, 565.

[294]For a monograph, see Valters; Flitsch *Ring-Chain Tautomerism*; Plenum: New York, 1985. For reviews, see Valters *Russ. Chem. Rev.* **1973**, *42*, 464-476, **1974**, *43*, 665-678; Escale; Verducci *Bull. Soc. Chim. Fr.* **1974**, 1203-1206.

Exhibit 3

ADVANCED ORGANIC CHEMISTRY

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